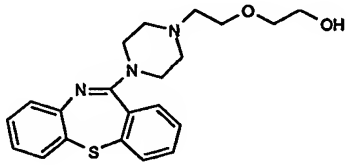
PREPARATION OF QUETIAPINE

Field of the invention

11-(4-[2-(2-hydroxyethoxy)ethyl]-1-piperazinyl]dibenzo[b,f]-1,4-thiazepine (I) is a well established drug substance known under the INN name quetiapine.



I

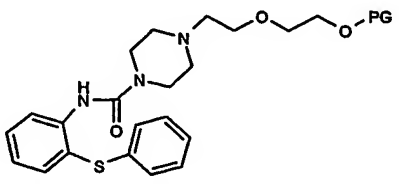
It is used as an antipsychotic or neuroleptic. The present invention provides an economical alternative method for the preparation of quetiapine in high yield and purity. Further objects of the invention are novel intermediates useful in the process according to the invention.

Background of the invention

Several methods for the preparation of quetiapine are known, as disclosed in e.g. GB 8607684, GB 8705574, and WO 01/55125. The known methods involve reacting a halo derivative (e.g. iminochloride) of dibenzo[b,f][1,4]-thiazepin-11(10-H)-one with 1-[2-(hydroxyethoxy)-ethyl]piperazine; reacting the aforementioned halo derivative with piperazine and reacting the resulting intermediate with a haloethoxyethanol; and reacting a haloethylpiperazinylthiazepine derivative with ethylene glycol.

Summary of the invention

According to the present invention, the target compound I is obtained by cyclizing a compound of formula II

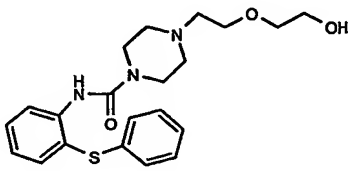


II

wherein PG represents a protective group, and subsequently removing the protective group.

The compound of formula II is prepared either

a) by attaching the protective group PG to the hydroxyl group of compound III

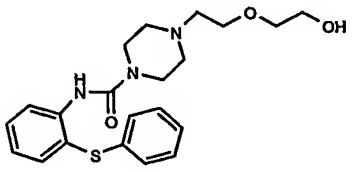


III

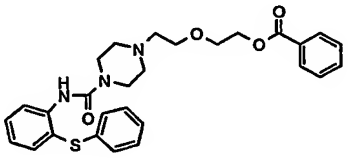
which may be prepared by a one pot reaction involving 2-phenylsulfanylphenylamine, 1-[2-(hydroxyethoxy)-ethyl]piperazine and a coupling agent, e.g. phosgene or equivalent; or

b) by attaching the protective group to the hydroxyl group of 1-[2-(hydroxyethoxy)-ethyl]piperazine prior to reaction with 2-phenylsulfanylphenylamine and the coupling agent.

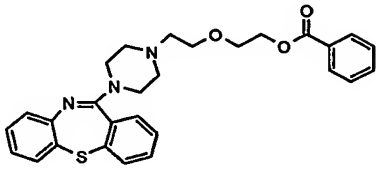
Further objects of the invention are the novel intermediates III, IV and V:



III



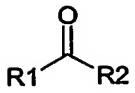
IV



V

Disclosure of the invention

2-phenylsulfanylphenylamine may be prepared e.g. by reacting 1-chloro-2-nitrobenzene with benzenethiol and catalytically reducing the nitro group, e.g. as disclosed in the literature. According to the method of the present invention, compound III or IV is obtained without isolation of intermediates by allowing 2-phenylsulfanylphenylamine to react with a carbonyl compound VI



VI

wherein R1 and R2 may independently be halo, p-nitrophenyl, imidazolyl or -OR wherein R is alkyl or aryl,
and adding 1-[2-(hydroxyethoxy)-ethyl]piperazine either as such or with a protective group on the hydroxy group. Preferred carbonyl compoumds VI include phosgene, diphosgene, triphosgene, (p-nitro)phenylchloroformate, methylchloroformate, dimethyl carbonate and carbonyldi-imidazole. Preferred protective groups inlude ethers and esters, e.g. benzoyl, acetyl, benzyl and tetrahydropyryl.

The reaction of 2-phenylsulfanylphenylamine with the compound of formula VI is preferably carried out in a suitable solvent; preferably toluene, but other aromatic and aliphatic hydrocarbons, also chlorinated derivatives, may be used. The reaction temperature may range from - 50 °C to 25 °C. The subsequent reaction with protected or unprotected 1-[2-(hydroxyethoxy)-ethyl]piperazine is preferably carried out at - 10 °C to 25 °C in the presence of a base, preferably triethylamine but other bases, e.g. other tertiary amines, may be used.

In the case 1-[2-(hydroxyethoxy)-ethyl]piperazine is used in the above step without a protective group, the protective group PG is subsequently introduced to yield compound II. Preferably, benzoyl chloride is used; other alternatives include acid chlorides and anhydrides, as well as ether-forming reagents. The reaction is preferably carried out at a temperature of 0-100 °C, preferably at ambient temperature.

Compound II is cyclized by treatment with a ring closure agent. Such agents include phosphorus oxychloride, phosphorus pentoxide and polyphosphoric acid. An advantageous reagent is a mixture of phosphorus oxychloride and phosphorus pentoxide, preferably using an excess of phosphorus oxychloride as a solvent.

Possible co-solvents are aliphatic or aromatic hydrocarbons, preferably toluene, as well as chlorinated hydrocarbons. The preferable temperature ranges from 50 to 130 °C, preferably about 80 - 100 °C.

Following cyclization, the protective group on the hydroxyl moiety is removed to produce the target compound I, which can be further transferred to a pharmaceutically acceptable salt thereof. If the protective group is susceptible to hydrolysis in basic conditions, sodium hydroxide in ethanol at 20 - 100 °C is preferably used.

Examples

Example 1. 4-[2-(2-hydroxyethoxy)-ethyl]-piperazine-carboxylic acid (2-phenylsulfanyl-phenyl)-amide

The reaction was carried out without isolation of intermediates in a one pot synthesis. Toluene (30 ml) and phosgene solution (20% in xylene, 9.1 ml, 17.16 mmol) were charged into a reaction flask. The mixture was cooled to -50°C. A mixture of 2-phenylsulfanylphenylamine (3 g, 14.9 mmol), triethylamine (2.4 ml, 17.1 mmol) and toluene (5 ml) was charged into the reaction flask at -50°C during 5 min. The mixture was allowed to reach room temperature and it was stirred at room temperature for 1.5 h. Then the reaction mixture was added to another reaction flask at -10-0 °C, containing the cooled mixture of 1-[2-(hydroxyethoxy)-ethyl]-piperazine, triethylamine (2.7 ml) and toluene (20 ml). The reaction mixture was stirred at room temperature for 1.5 h. Precipitated triethylamine hydrochloride was filtered off. The resulting toluene solution was washed twice with saturated NaCl-water (10 ml), dried with K_2CO_3 and evaporated *in vacuo*. The yield of 4-[2-(2-hydroxyethoxy)-ethyl]-piperazine-carboxylic acid (2-phenylsulfanyl-phenyl)-amide was 4.76 g.

^{1}H NMR ($CDCl_3$). 2.35 (4H, m), 2.53 (2H, t), 3.34 (4H, t), 3.60 (4H, m), 3.67 (2H, t), 7.0-7.63 (9H, m). ^{13}C NMR ($CDCl_3$). 43.5, 52.8, 57.7, 61.8, 67.7, 72.4, 115.3, 118.4, 122.8, 125.4, 126.1, 126.3, 126.4, 127.8, 128.9, 129.2, 131.2, 141.2, 153.9

Example 2. Benzoic acid 2-{2-[4-(2-phenylsulfanyl-phenylcarbamoyl)piperazin-1-yl]-ethoxy}-ethyl ester

4-[2-(2-hydroxyethoxy)-ethyl]-piperazine-carboxylic acid (2-phenylsulfanyl-phenyl)-amide (4 g, 10 mmol), triethylamine (2 ml, 15 mmol) and toluene (50 ml) were charged into a reaction flask. Benzoyl chloride (1.7 g, 12 mmol) in toluene (5 ml) was added at 0-10 °C. The mixture was stirred for 16 h at 20 °C. Cold water (50 ml) and 1 M NaOH (10 ml) were added. The mixture was stirred for 20 min. The water phase was separated. The organic phase was washed with saturated NaCl solution (25 ml) and evaporated *in vacuo*. The yield of benzoic acid 2-{2-[4-(2-phenylsulfanyl-phenylcarbamoyl)piperazin-1-yl]-ethoxy}-ethyl ester was 4.91 g. ^{1}H NMR ($CDCl_3$). 2.35 (4H, m), 2.54 (2H, m), 3.28 (4H, m), 3.63 (2H, m), 3.77 (2H, m), 4.47 (2, m), 7.0-8.3 (14H, m). ^{13}C NMR ($CDCl_3$). 43.7, 53.0, 57.6, 63.9, 68.9, 69.0, 118.4, 119.8, 122.7, 126.5, 127.1, 129.2, 129.3, 129.6, 130.0, 131.0, 133.1, 135.6, 136.0, 136.5, 140.1, 141.3, 154.0, 166.4

Example 3. Benzoic acid 2-[2-(4-dibenzo[b,f][1,4]-thiazepin-11-yl-piperazin-1-yl]-ethoxy]-ethyl ester

Benzoic acid 2-{2-[4-(2-phenylsulfanyl-phenylcarbamoyl)piperazin-1-yl]-ethoxy}-ethyl ester (2 g, 3.96 mmol), phosphorus oxychloride (15 ml) and phosphorus pentoxide (2 g) were charged into a reaction flask. Then the mixture was stirred at 90 °C for 19 h. Phosphorus oxychloride was evaporated *in vacuo*. Dichlorometane (20 ml) and ice-water (20 ml) were added to the residue. $NaHCO_3$ was added until the pH was 7-8. The organic phase was separated, washed with saturated NaCl-water (10 ml), dried with Na_2SO_4 and evaporated. Yield of benzoic acid 2-[2-(4-dibenzo[b,f][1,4]-thiazepin-11-yl-piperazin-1-yl]-ethoxy]-ethyl ester 1.53 g. ^{1}H NMR ($CDCl_3$). 2.52-2.67 (6H, m), 3.67-3.80 (8H, m), 4.47 (2H, m), 6.90-8.0 (13H, m). ^{13}C NMR ($CDCl_3$). 46.1, 53.4, 63.7, 68.9, 69.0, 69.1, 122.7, 125.4, 127.1, 128.2, 128.4, 129.0, 129.1, 129.2, 129.6, 129.7, 130.0, 130.7, 131.1, 132.1, 133.0, 134.1, 139.8, 160.7, 166.5

Example 4. Quetiapine

Benzoic acid 2-[2-(4-dibenzo[b,f][1,4]-thiazepin-11-yl-piperazin-1-yl]-ethoxy]-ethyl ester (1.5 g, 2.97 mmol), ethanol (10 ml) and 50% NaOH (1 ml) were charged into a reaction flask. Then the mixture was stirred at 80 °C for 2 h. The reaction mixture was evaporated *in vacuo*. Ethyl acetate (20 ml) and saturated NaCl-water (15 ml) were added to the residue. The water phase was separated. To the organic phase was added 1 M HCl (10 ml). To the combined water phase was added 50% NaOH until the pH was 12 and saturated NaCl-water (10 ml). The alkaline water phase was extracted twice with ethyl acetate (10 ml). The combined organic phase was washed with saturated NaCl-water (10 ml), dried with Na_2SO_4 and evaporated. Yield of quetiapine 0.93 g.